

## REMARKS

The Applicants respectfully request entry of the amendments set forth above and reconsideration and withdrawal of the restriction requirement, objections, and the claim rejections in view of the amendments and the following remarks.

### Restriction Requirement

Applicants maintain their traversal of the restriction requirement for the reasons set forth in the previous office action responses and respectfully request reconsideration and withdrawal of the restriction requirement and request that examination of the claims be expanded consonant with their scope prior to restriction.

### Rejections under 35 U.S.C. 112, first paragraph

Claims 121-123, 139-140, 144-145, 150-155 and 157-161 remain rejected under 35 U.S.C. 112 as failing to comply with the written description requirement. Specifically, the Examiner alleges that the specification fails to describe the genus of claimed fragments of the polypeptide of SEQ ID NO: 2, fragments of the fragments, fragments of polypeptides with “limited structural similarity to the polypeptide of SEQ ID NO: 2”, and sequence variants of the aforementioned fragments (Office Action, p. 3). Applicants note that the Examiner’s comments regarding alleged failure to meet the written description requirement referred only to “fragments”. Applicants also note that the Office Action specifically indicated that “any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant’s response and withdrawn.” (Office Action, p. 2). Applicants have framed their remarks accordingly.

Applicants respectfully disagree with the Examiner’s contention that “the instant specification did not describe the genus of claimed fragments...and therefore the claims, which encompass the various fragments of the polypeptide of SEQ ID NO: 2 do not meet the written description provision...” (Office Action, p. 3). Applicants also respectfully disagree that “the instant specification did not describe the structure within the polypeptide of SEQ ID NO: 2, which is critical for formation of ordered aggregates...” (Office Action, p. 4). The specification discloses that amino acid composition rather than any particular conserved

sequence underlies the property of self-coalescence. Thus one structural feature of self-coalescing sequences is that they are rich in the amino acids glutamine, asparagine, glycine, and possibly the polar residues serine and tyrosine (specification, p. 61, lines 26-30 and lines 11-14; and paragraph bridging pp. 8-9). It will be appreciated that the sequence can be enriched for one or more of these amino acids in different combinations, e.g., glutamine and asparagine, glutamine and glycine, etc. The specification describes examples of such combinations. Applicants draw the attention of the Examiner to Examples 5 and 6 (specification, pp. 59-69), which describe BLAST searches of Genbank that were performed using the prion-forming regions of SEQ ID NO: 2 (amino acids 1-114) and SEQ ID NO: 4 (amino acids 1-65) as query sequences in order to identify polypeptides that contain similar domains that would be expected to self-coalesce. The identified polypeptide regions have limited sequence identity to the query sequences but are enriched for the aforementioned amino acids. Thus, suitable degrees of enrichment are exemplified by amino acids 1-114 of SEQ ID NO: 2, amino acids 1-65 of SEQ ID NO: 4, and the regions identified in SEQ ID NOs: 22-36 as described in Examples 5 and 6. Applicants respectfully point out that at least 7 of these sequences were tested and shown to have properties indicative of self-coalescence, notwithstanding their limited identity to the query sequences.

The specification teaches that “the critical prion-determining domains of SEQ ID NOs: 2 and 4 have an unusually high concentration of the polar residues glutamine and asparagine and are predicted to have very little secondary structure” (specification, p. 68, lines 24-26). The specification also teaches that, “the secondary structure of all proteins that form amyloid fibrils under physiological conditions is partially random coil in aqueous solutions” (p. 82, lines 9-10). As will be appreciated by one of skill in the art, the random coil is a polymer conformation where the monomer subunits are oriented randomly while still being bonded to adjacent units. It is not one specific shape, but a statistical distribution of shapes for all the chains in a population of macromolecules. While aggregates formed by SCHAG polypeptides typically are rich in  $\beta$ -sheet structure (specification, p. 6, lines 30-31), this  $\beta$ -sheet rich secondary structure is a characteristic of the aggregates rather than individual polypeptides. Applicants submit that in light of these teachings it would not be reasonable to require them to describe a conserved secondary structure that serves to identify the claimed embodiments, which encompass polypeptides that are not present in such aggregates.

The Examiner states that, “Applicant appears to be taken (*sic*) the position that 35 U.S.C. 112, first paragraph, permits an artisan to present claims of essentially limitless breadth as long as the specification provides one with the ability to test any particular embodiment, which is encompassed within the material limitation of a claim and thereby distinguish between those embodiments which meet the functional limitations from those embodiments which don’t. However, this “make and test” approach does not satisfy the written description requirement... (Office Action, p. 4). Applicants respectfully note that (i) the claims are not of “limitless breadth” since they recite fragments of specific sequences and fragments of variants of these sequences; and (ii) the specification provides considerable guidance as to the characteristics of fragments that would be expected to self-coalesce.

Furthermore, Applicants respectfully submit that the Examiner does not give sufficient weight to the “make-and-test” approach as a means of providing written description, particularly in the context of a specification that provides the artisan with guidance as to suitable characteristics of the molecules to be made and tested, as does the instant specification. Applicants respectfully draw the Examiner’s attention to Applicants’ remarks in the previous office action response (filed December 22, 2006) regarding the holding in *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052, 77 U.S.P.Q. 2d 1161 (Fed. Cir. 2005). Applicants submit that this case clearly shows that a specification that provides a representative embodiment and permits the artisan to “make and test” and thereby distinguish embodiments that fall within the scope of the claims from those embodiments that do not, can provide sufficient written description support for claims to a polypeptide in terms of its function. While not conceding that the “make-and-test” approach by itself would not suffice to satisfy the written description requirement, Applicants *do not rely solely on the “make-and-test” approach to satisfy the written description requirement* in the absence of disclosure of identifying characteristics of the claimed embodiments, as suggested by the Examiner (Office Action, p. 4). Instead, Applicants do provide such identifying characteristics, as indicated above. Applicants do, however, submit that the Examiner has improperly discounted the contribution of the “make-and-test” approach to meeting the written description requirement.

Applicants also respectfully point out that, “there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.” *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). The Examiner has acknowledged that the written description requirement may be satisfied by providing “partial structure, physical and/or chemical properties, functional characteristics, ...or any combination thereof” (Office Action, p. 4). Applicants submit that specification’s teachings regarding amino acid composition and examples of self-coalescing sequences having such composition provide sufficient written description support for the presently claimed fragments.

The Court of Appeals for the Federal Circuit (CAFC) has held that “Compliance with the written description requirement is essentially a fact-based inquiry that will ‘necessarily vary depending on the nature of the invention claimed.’” *Enzo*, 323 F.3d at 963, 63 USPQ2d at 1612 (Fed. Cir. 2002), quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). The specification teaches and provides many working examples showing that amino acid composition rather than primary sequence and/or a particular conserved secondary structure are important determinants that confer self-coalescing properties on a polypeptide. These facts distinguish the instantly claimed invention from typical polypeptide claims, wherein the function often depends critically on the identity of one or a few specific amino acid residues and/or precise secondary structure. Applicants submit that the nature of the claimed invention must be properly taken into account in determining whether the written description requirement has been met.

In summary, Applicants respectfully submit that their detailed description of methods for making and testing, in combination with the other identifying characteristics described above, satisfy the written description requirement with respect to the claims as pending prior to the instant amendments. Nonetheless, solely in order to further prosecution and without waiver, disclaimer, or prejudice, Applicants have amended claim 150 to recite in part as follows (wherein added text is underlined): (c) fragments of (a) that self coalesce into ordered aggregates and include at least 50 amino acids the N domain of SEQ ID NO: 2; (c') fragments of (b) that are at least 50 amino acids long and self coalesce into ordered aggregates;...(e) sequence variants of (a), (b), (c), or (c'), wherein sequence variations from (a)-(c') consist of addition, deletion, or substitution of 1-20 amino acids with the proviso that

said variants of the fragments of (c) and (c') retain at least an equal enrichment for amino acids that promote self-coalescence (G+N+Q+S+Y) as does the original sequence of (c) or (c'), and that self-coalesce into ordered aggregates. Support for the amendment is found e.g., at p. 61, lines 26-29, indicating that sequences of 50-150 amino acids that are rich in certain amino acid residues (e.g., glycine, glutamine, asparagines, serine, tyrosine) are a conserved feature of prion-like proteins (which, as noted throughout the specification, exhibit self-coalescing properties). See also, p. 8, lines 29-31, noting the importance of glutamine, asparagine, serine and tyrosine. It will be understood that the N domain refers to amino acids 2-113 of SEQ ID NO: 2 (specification, p. 10, line 18).

In addition, solely in order to further prosecution and without waiver, disclaimer, or prejudice, Applicants have amended claim 144 to recite that the fragment includes at least 50 amino acids of the N domain of SEQ ID: 2. Support for the amendment is found, e.g., in the afore-mentioned portions of the specification and the teaching that the glutamine+asparagine rich N domain is the prion-forming domain of SEQ ID NO: 2 (p. 51, lines 11-14).

While Applicants continue to maintain the claims satisfied the written description requirement prior to the instant amendment, Applicants respectfully submit that the instant amendments render the Examiner's contention that, "the claims do not require that the recites (*sic*) fragments possess any particular conserved structure or other disclosed distinguishing feature, which supports the ability of the fragments to form ordered aggregates." (Office Action, p. 3) moot. Withdrawal of the rejection of claim 150, claim 144, and claims 121-123, 139-140, 145, 151-155, and 157-161, which are dependent on claim 150 or 144, is respectfully requested.

#### Rejections under 35 U.S.C. 112, second paragraph

Claim 130 stands rejected under 35 U.S.C. 112, second paragraph, as allegedly being vague and indefinite for the recitation of "appears substantially the same". Applicants respectfully disagree that this phrase renders the claim vague and indefinite. Applicants respectfully submit that one of ordinary skill in the art would understand the meaning of the phrase in the context of the specification and claims. Applicants note that the CAFC has held the term "substantially" to be definite. In *Andrew Corp. v. Gabriel Electronics*, the court held that the limitation "which produces *substantially equal* E and H plane illumination

patterns” was definite because one of ordinary skill in the art would know what was meant by ‘substantially equal’.” *Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988). Applicants submit that in light of this holding, it is evident that the phrase “appears substantially the same” should be considered definite. Applicants draw the Examiner’s attention to Example 9 of the specification, in which fiber appearance of NM mutants were studied by electron microscopy and Congo red binding. Many mutants were found to have “wild type” (wt) appearance while several were found to differ in fiber appearance (see pp. 85-87). Applicants respectfully submit that one of skill in the art would understand “appear wild type” to mean “appear substantially the same as wild type”. Thus, if one of skill in the art were in doubt as to what is meant by “appear substantially the same”, the artisan could use the appearance of any of the mutants identified as having fiber morphology “as wt” in Table 1 (p. 86), as compared with the appearance of fibers formed by wild type NM, as a standard to determine what is meant by “appears substantially the same”. Withdrawal of the rejection is respectfully requested.

Claims 132-133 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly being vague and indefinite for the recitation “except at position 2”. The Examiner states that the “metes and bounds of the recitation cannot be determined...” (Office Action, p. 7). Applicants submit that the phrase “except at position 2” is clear. The relevant sequence could have any amino acid at position 2 except the amino acid that is found at position 2 in SEQ ID NO: 2. Applicants find the rejection confusing and respectfully submit that it is unclear in what sense the Examiner finds that the metes and bounds cannot be determined. Applicants interpret the rejection as suggesting that the claim did not make it clear whether “position” refers to position within the amino acid sequence or position within the polypeptide. Applicants have amended claims 132 and 133 to indicate that “position” refers to the position in the amino acid sequence. Applicants note that claims 124 and 127 (on which claims 132 and 133, respectively, depend) have been amended to recite that the position corresponds to position 2 (or 184) of SEQ ID NO: 2, as discussed below (see section entitled “Claim objections”). Claims 132 and 133 have been likewise amended for consistency. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. 102

Claims 121-122, 139, and 144 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kushnirov, et al., *Yeast*, 6:461-472, 1990. Applicants continue to disagree with the Examiner's reasoning set forth in section 10 of the Office Action and in earlier office actions. Applicants point out once again that the claims are not drawn to every polypeptide that self-coalesces to form higher ordered aggregates and that comprises *any* fragment of SEQ ID NO: 2. Instead, the claims indicate that *the fragments* self-coalesce (emphasis added). Applicants note that the Examiner evidently found this argument persuasive in withdrawing the rejections over the Glabe reference and over Prusiner, et al., U.S. Pat. No. 5,962,669, and submit that the rejection over Kushnirov should likewise have been withdrawn. Applicants further respectfully submit that the rejection is moot in view of the amendment to claim 144 since the fragment cited by the Examiner does not include at least 50 amino acids of the N domain of SEQ ID: 2 as recited in the instant claim. Withdrawal of the rejection is respectfully requested.

Claims 139-140, 144-145, 150-155, and 157-161 stand rejected under 35 U.S.C. 102(e) as being anticipated by Prusiner, et al., U.S. Pat. No. 6,277,970. Applicants continue to disagree with the Examiner's reasoning set forth in section 12 of the Office Action and in earlier office actions. Applicants note that the Examiner evidently found Applicants' arguments persuasive in withdrawing the rejections over the Glabe reference and over Prusiner, et al., U.S. Pat. No. 5,962,669, and submit that the rejection over U.S. Pat. No. 6,277,970 should likewise have been withdrawn. Applicants further respectfully submit that the rejection is moot in view of the amendments to claims 144 (for reasons stated in the preceding paragraph) and 150 (since claim 150 now clearly indicates that the self-coalescing fragments are longer than the fragments of 2 and 3 amino acid length cited by the Examiner). Withdrawal of the rejection is respectfully requested.

### Claim objections

Claims 124-129, 131, 134, 135, 137, and 138 are objected to on the ground that they encompass polypeptides of SEQ ID NO: 2 with amino acid substitutions at specific positions within SEQ ID NO: 2 which, according to the Examiner, results in a different polypeptide and necessitates assignment of a different SEQ ID NO. Claims 125-126, 128-129, 131, 134-135, and 137-138 all depend on claim 124 or 127. Applicants respectfully note that claims 124 and 127 have been examined at least twice previously without this objection having been made and respectfully submit that assignment of new SEQ ID NOs is not required or even helpful in order to allow a meaningful search or comparison to be made. Applicants have amended claim 124 to recite that the reactable side chain is present at the position in the SCHAG amino acid sequence that corresponds to position 2 of SEQ ID NO: 2 and have amended claim 127 to recite that the reactable side chain is present at the position in the SCHAG amino acid sequence that corresponds to position 184 of SEQ ID NO: 2. Applicants submit that one of skill in the art would clearly understand this to be the intended meaning of the language present in the claims prior to the amendment. Since the claimed polypeptide comprises a SCHAG amino acid sequence that is at least 90% identical to amino acids 2 to 253 of SEQ ID NO: 2, Applicants submit that the position in the SCHAG amino acid sequence that corresponds to position 2 or position 184 of SEQ ID NO: 2 will be readily apparent, and SEQ ID NO: 2 can be used to perform the search. Applicants submit that in such a search, polypeptides comprising amino acid sequences at least 90% identical to SEQ ID NO: 2 would be identified. These polypeptides could then be assessed to determine whether they fall within the scope of the claims. Applicants respectfully request withdrawal of the objection.

### CONCLUSION


For the foregoing reasons Applicants respectfully request that the rejections and objection be withdrawn and that the claims be allowed. Applicants also respectfully request that the restriction requirement be withdrawn and the claims examined consonant with their scope prior to restriction.

If this response requires any fee or a petition for extension of time that has not been filed herewith, then please consider this a request for such extension of time and charge any fees due to charge Marshall, Gerstein & Borun, LLP, deposit account number 13-2855, under matter number 30554/34978A.

Respectfully submitted,

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